PEER-REVIEW REPORT 1

Name of journal: Neural Regeneration Research
Manuscript NO: NRR-D-18-00556
Title: The pig as a preclinical traumatic brain injury model: current models, functional outcome measures, and translational detection strategies
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Date sent for review: 2018-08-14
Date reviewed: 2018-08-29
Review time: 15 Days

COMMENTS TO AUTHORS

The review addresses an important and interesting area of traumatic brain injury (TBI). It suggests that the current lack of effective treatment for TBI may be due to the inappropriate preclinical brain injury models, in particularly rodents being used in the research field. Therefore, this review suggests the pig maybe a better preclinical model for TBI, which may improve the success of developing effective therapies for TBI.

Overall, the review is well written and with a good cover of the research carried out on pig/piglets with brain injury. However, there are a few major concerns that should be addressed to convince the reader that the pig is a better preclinical TBI model than the rodents.

1) The authors mentions the similarities of the pig with the human brain in regards to size, structure and composition. However, there is no data to demonstrate it has a similar pathophysiological response after injury. The difference in components within the pig brain such as neurons and glial cells, immune response, vasculature, etc may be sufficiently different to produce a different response after a traumatic injury compared to human. The authors mention how different rodents data are to human data, but fail to provide similar data of pig data with human. One potential area to discuss this is at the biomarker section (line 406). Since NSE and other biofluid biomarkers, and neuroimaging have been carried out in both pig and human TBI, how are these data in pig compare to human data?

2) The authors mention the differences between different studies. I think the reviewer should speculate in the review why there are differences between studies. Is it the injury model or the difference in animal strains or size that is making the data not reproducible between laboratories/groups?

3)(line 170) Loss of consciousness (LOC) and decreased CBF and CPP are not good objective methods to determine if DAI or not, since any type of injury to the head if severe enough would result in LOC.

4) As a review, the authors should provide a summary of the pros and cons of the various behavioural tests used. Even better, if can highlight which potential 'gold standard' behavioural test(s)' researchers should use.